Synthesis Characterization and Biological Screening of Tri-benzyl tin(IV) Complexes of Some Schiff Bases

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Synthesis and characterization of some novel di and tri-benzyl tin(IV) complexes of some Schiff bases are reported. The ^{1}H-NMR, ^{13}C-NMR, ^{119}Sn-NMR, IR, Elemental Analysis and ^{119}Sn Mössauber studies are made for structural determination. Spectroscopic data reveals that the ligand molecule is bound to the tin atom through oxygen. On the basis of spectroscopic data tetrahedral geometry is proposed for the synthesized compounds. The synthesized compounds have been tested against various microorganisms. The results obtained show that the synthesized compounds have promising activity against all the tested micro-organisms.

Keywords: Schiff base; Organotin(IV) complexes; Tri-benzyl tin; Activity; Spectra.

INTRODUCTION

Schiff bases play an important role as ligands due to their ease of preparation and reactivity in organometallic chemistry.[1] Schiff base complexes of organotin(IV) moieties have been widely investigated and show excellent activity as fungicides, bactericides, anti-inflammatories, and as PVC stabilizers.[2-4] The increase of the industrial, agriculture and biological applications of organotin(IV) compounds during the last few decades has led to their accumulation in the environment and finally in the biological systems. However, the high phytotoxicty of these compounds towards many plants has restricted their practical use.[5] The most recent development in the field of organotin(IV) chemistry is their use as anti-tumor agents. Many di and tri-organotin(IV) complexes exhibit maximum anti-tumor activity combined with low toxicity.[6-10] The importance of organotin moieties has been further enhanced during the past few decades due to their complexes with biologically important compounds.[11-27] In a previous paper we synthesized organotin(IV) complexes of Male-imido-Acetic acid.[28] As a continuation, we are reporting synthesis, characterization and biological elucidation of tri-benzyl tin(IV) complexes of some reported Schiff bases.[29]

EXPERIMENTAL

All the reactions were carried out under anhydrous and oxygen free atmosphere. The solvents used were dried before use according to the literature method.[30] The Schiff base tri-benzyl and I tin(IV) chloride were prepared according to the methods provided in the literature.[29,31] Schiff base II (compound II) was prepared by refluxing salicyldehyde and ethylenediamine (2:1) in benzene for 3 hours; the water molecules formed during the reaction were removed aziotropically using Dean's stark apparatus. The solid mass formed was recrystalized from dry acetone.

The melting points were measured on a Reichert thermometer of F. G. Bode Co., Austria. IR spectra were obtained in KBr using a Perkin Elmer FT IR-1605 Spectrophotometer. Elemental analyses were carried out on a Yanaco MT-3 high-speed CHN analyzer with antipyrene as a reference compound. The ^{1}H- ^{13}C- and ^{119}Sn NMR spectra were recorded on a multinuclear FT NMR 200 MHz of JEOL using TMS as an internal standard. Some of the ^{13}C spectra were measured on a Bruker AM 270 instrument at 50 MHz with ^{13}C probe. The Mössbauer spectra were recorded at 80 K on a Cryophysics instrument equipped with a 15 mCi Ca $^{119}SnO_3$ source.

Synthesis of Tri-benzyl tin(IV) Complexes of Schiff Bases

Tri-ethyl amine chloride (20 mM) was added to a solution of ligand (10 mM) dissolved in chloroform and the resulting mixture was refluxed for 2-3 hours; to this mixture tri-benzyl tin chloride (20 mM) in chloroform (50 mL) was

added with continuous stirring.

The mixture was again refluxed for 7-8 hours under nitrogen. White solid material formed during the reaction was filtered off. The filtrate was concentrated under vacuum. The solid obtained was recrystallized from a mixture of 1:1 v/v (50 mL) acetone and petroleum ether (40-60 °C). Products obtained were kept under nitrogen for further study.

Anti Bacterial Activity

The antibacterial activities were determined by using the agar well diffusion method.[32] The wells were dug in the media with a sterile borer and an eight-hour-old bacterial inoculums containing ca. $10^4 - 10^6$ colony-forming units (CFU)/mL was spread on the surface of the nutrient agar using a sterile cotton swab. The recommended concentration of the test sample (2 mg/mL in DMSO) was introduced into the respective wells. Other wells containing DMSO and the reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated immediately at 37 °C for 20 h. The activity was determined by measuring the diameter of the inhibition zone (in mm) showing complete inhibition. Growth inhibition was calculated with reference to the positive control.

Antifungal Activity

The different concentrations (50, 100, 250 and 500 ppm) of the test compounds I, II & III were used to study the effect on germination of *C. glocoporiodes*, *A. brassicicola*, *A. brassicae*, *C. capsici* and *H. graminium* by the hanging drop method developed by Brine.[33] The germination of spores was observed under the microscope after 8 hours of incubation. The percentage inhibition of spore germination was calculated as

$$\text{Percentage inhibition of spore germination} = \frac{\text{Total no. of ungerminated spores}}{\text{Total no. of spores}} \times 100$$

Acute Toxicity

ALD50 (average lethal dose at 50% survival) of the compounds was determined in albino mice. The mice of either sex (body weight 20-25 g) were used. The test compound was injected intraperitoneally at different dose levels in groups of 10 animals and percent mortality in each group was observed after 24 h of drug administration. The ALD50 value (1 mg kg^{-1}) was calculated from the data obtained by the method of Smith.[34]

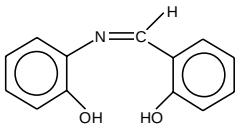
RESULTS AND DISCUSSION

Schiff base 1 and the tri-benzyl tin chloride were prepared according to the literature methods.[29,31] Schiff base 2 (compound I) was prepared by refluxing salicyldehyde and ethylenediamine (2:1) in benzene for 3 hours (Eqn 1). The tri-benzyl tin(IV) complexes of Schiff bases 1 & 2 were prepared by refluxing Schiff bases 1 & 2, tri-ethyl amine, and tri-benzyl tin chloride in chloroform (Eqn 2).

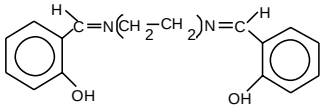
$$C_7H_6O_2 + {}_2HN\text{-}(CH)_2\text{-}NH_2 \rightarrow C_{16}H_{16}N_2O_2 + H_2O. \quad (1)$$

$$1L + 2Bz_3SnCl + Et_3N \rightarrow 2Bz_3SnL + 2Et_3N.HCl. \quad (2)$$

Where L = Schiff base 1 and Schiff base 2.



Schiff Base 1.



Schiff Base 2.

(Compound 1)

Physical parameters and the spectroscopic data

Compound I

Recrystallized from acetone, mp: 87 °C, yield: 85%, solubility: soluble in chloroform and acetone. CHN analysis: the calculated values are given in parentheses. C: 71.62 (71.64), H: 5.97 (5.89), N: 10.42 (10.44), ^{1}H NMR ($CDCl_3$): H-1: 8.02 d (8); H-2: 7.11 d (8); H-3: 7.46 d; H-4: 7.2 d (8); H-7: 9.1 S; H-8: 3.7 t (7). ^{13}C NMR ($CDCl_3$): C-1: 152.6; C-2: 148.3; C-3: 129.5; C-5: 127.34; C-6: 129.1; C-7: 133.8; C-8: 25.8. IR (KBr, Cm^{-1}): 3050 (CH ar), 1680 (νC=N), 3315 (OH).

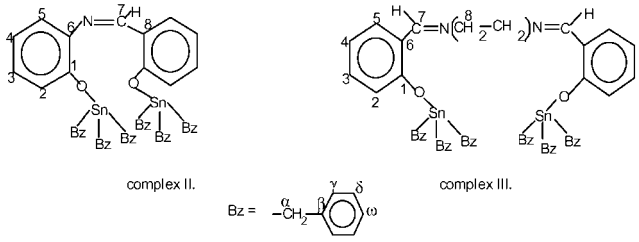
Compound II

Recrystallized from chloroform and petroleum ether (40-60 °C), Melting Point: 159 °C. Yield: 83%, Molecular formula: $C_{40}H_{32}N_2O_4Sn$, Molecular wt: 724. CHN analysis: C: 66.27 (66.30), H: 4.40 (4.41), N: 1.91 (1.93). Sn: 16.55 (16.58). IR (KBr, cm^{-1}): 3038 (ν CH aromatic), 1678 (νC=N), 535 (νSn-O), 480 (νSn-C). ^{1}H NMR ($CDCl_3$): H-2: 7.7 d (8); H-3: 7.2 d (8); H-4: 7.15 d (8); H-5: 7.5 d (8); H-7: 9.1 S; H-8: 7.8 d (8). H-α: 1.25 S: H-β: H-γ:, H-δ:, H-ω: 7.35-7.40 m. ^{13}C NMR ($CDCl_3$): C-1: 154.7; C-2: 141.6; C-3: 138.7; C-4:

128.9; C-5: 140.8; C-6: 135.6; C-α: 29.5; C-β: 132.5; C-γ: 129.8; C-δ: 133.8; C-ω: 123.1. ^{119}Sn NMR ($CDCl_3$): -22.1 ppm. ^{119}Sn Mössbauer (mm^{-1} s 80 K): Q.S: 3.80; I.S: 1.38; Γ_1: 1.10; Γ_2: 1.12. QS = Quadrupole splitting; IS = Isomer shift; Γ_1 & Γ_2 = Line widths.

Compound III

Recrystallized from acetone and petroleum ether (40-60 °C). Melting Point: 177 °C. Yield: 75%, Molecular formula: $C_{58}H_{56}N_2O_2Sn_2$, Molecular wt: 1052. CHN analysis: C: 66.13 (66.15), H: 5.30 (5.32), N: 2.63 (2.66), Sn: 22.79 (22.81). IR (KBr, cm^{-1}): 3042 (ν CH aromatic), 1683 (νC=N), 527 (νSn-O), 447 (νSn-C). ^{1}H NMR ($CDCl_3$): H-2: 7.8 d (8); H-3: 7.10 d (8); H-4: 7.05 d (8); H-5: 7.6 d (8); H-7: 8.9 S; H-8: 3.5 t (7). H-α: 2.1 S: H-β:, H-γ:, H-δ:, H-ω: 7.65-7.78 m. ^{13}C NMR ($CDCl_3$): C-1: 155.0; C-2: 141.8; C-3: 138.8; C-4: 129.1; C-5: 141.2; C-6: 136.2; C-7: 122.4; C-8: 143.1; C-9: 134.2; C-α: 30.1; C-β: 134.4; C-γ: 128.4; C-δ: 127.1; C-ω: 123.8. ^{119}Sn NMR ($CDCl_3$): -170.0 ppm. ^{119}Sn Mössbauer (mm^{-1} s 80 K): Q.S: 3.77; I.S: 1.40; Γ_1: 0.98; Γ_2: 1.05. QS = Quadrupole splitting; IS = Isomer shift; Γ_1 & Γ_2 = Line widths.



Proposed Structure for Complexes II & III

Spectral Results

The ^{1}H NMR chemical shifts have been shown to be very important in structure elucidation of the coordination number and geometries of organotin(IV) compounds.[35-36] The aromatic protons are in the range of 7.2-7.8 ppm; the up fielding of aromatic protons is due to ring current effect. The azomethinic protons resonate at 8-9-9.1 ppm, respectively, which is in accordance with the earlier reported compounds.[37]

The ^{13}C NMR spectra of the synthesized compounds are properly resolved. The ^{13}C chemical shifts of the benzyl

Table 1. Anti bacterial bioassay results[a,b,c,d] for R_2SnL_2 and R_3SnL (inhibition zone in mm)

Micro-Organisms	Ligand 1	Ligand 2	*Cpd I	Cpd II	Standard Drug
Gram-Positive					
Bascillus subtilis	16	18	20	24	31
Staphlococcus aures	24	24	26	32	43
Gram-negative					
Escherichia coli	na	na	12	16	30
Shigella flexenari	10	12	16	18	33
Pseudomonas aeruginosa	12	14	16	20	25
Salmonella typhi	20	24	28	32	41

[a] Concentration used: 1.00 mg/1.00 mL of DMSO.
[b] Size of well: 6 mm (diameter).
[c] Standard drug: Imipinem.
[d] n.a: no activity.
* Cpd = compound.

Table 2. Toxic effect of compound I

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	++	+	+	+
C. gloeosporioides	++	+	na	na
A. brassicicola	++	+	+	+
A. brassicae	++	+	+	na
H. graminium	++	+	na	na

+ = low activity, ++ = medium activity, +++ = high activity, na = no activity.

groups attached to the tin are observed at the positions comparable with similar reported compounds.[38-40]

^{119}Sn chemical shift of organotin(IV) compounds cover a range of 600 ppm, for compound I ^{119}Sn signal is observed at -22.1 ppm and for compound II ^{119}Sn signal is observed at -170 ppm showing tetrahedral and octahedral geometry, respectively. The results obtained are in accordance with earlier reported compounds.[41-44]

^{119}Sn Mössbauer spectra are sensitive and the most important tool for the coordination number and for the geometry of organotin(IV) complexes.[45-48] ^{119}Sn Mössbauer quadrupole splitting (QS) value obtained for compound I is 2.88 mm^{-1} and for compound II is 3.88 mm^{-1} s. The data obtained prooves tetrahedral and octahedral geometry of the synthesized compounds.

In the IR spectra of the synthesized compounds the absorption bands for Sn-O & Sn-C are in consistent with earlier reported work.[49-53]

Biological Studies

Anti-bacterial activity

Antibacterial studies were performed against two Gram positive (*Bacillus subtilus*, *Staphloccus aureus*) and 4 Gram-negative (*Escherichia coli*, *Schigella flexenaria*, *Pseudomonas aeruginosa*, *Salmonella typh*) bacteria, and the results are summarized in Table 1. In order to compare the results obtained the Impinem is used as standard drug. The results obtained show that synthesized compounds have higher activity than the corresponding ligand but lower activity than the standard drug.

Anti fungal activity

Anti fungal results of the synthesized compounds are summarized in Tables 2-4. The results show significant activity at higher concentrations against all plant pathogens. The increase in toxicity of organotin(IV) compounds may be due to the coordination of tin(IV) atom with the oxygen of the ligands. The toxicity is also due to the lone pair of electrons on the oxygen and nitrogen, which may get free in solution and play a role in increasing the toxic effect of the synthesized compounds.

Acute toxicity studies

The ALD50 values of the studied tri-bezyl tin(IV) derivatives were found to be more than 400 mg kg^{-1} (the maximum dose tested), suggesting the safety margin of these derivatives.

Table 3. Toxic effect of compound II

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	+++	++	+	+
C. gloeosporioides	++	+	na	na
A. brassicicola	++	+	+	+
A. brassicae	+++	++	+	na
H. graminium	++	+	na	na

+ = low activity, ++ = medium activity, +++ = high activity, na = no activity.

Table 4. Toxic effect of compound III

Name of Fungi	% Inhibition (dose ppm)			
	500	250	100	50
C. capsici	++	+	+	na
C. gloeosporioides	+++	++	+	+
A. brassicicola	++	+	-	na
A. brassicae	+++	++	+	+
H. graminium	++	+	na	na

+ = significant activity, ++ = medium activity, +++ = high activity, na = no activity.

Table 5.

Compound	ALD50 (mg kg^{-1})
*Phenyl butazone.	> 500
Complex I.	> 400
Complex II.	> 400
Complex III.	> 400

* Standard drug.

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REFERENCES

1. Joshi, K. C.; Pathak, V. N.; Panwar, P. *Agic. Boil. Chem.* **1977**, *41*, 543.
2. Mehrotra, R. C.; Srivastava, G.; Saraswat, B. S. *Revs. Si, Ge, Sn, Pb compounds* **1982**, *6*, 171, and references cited therein.
3. Molloy, K. C. In *Bioorganotin Compounds*; Hartley, F. R., Ed.; The Chemistry of Metal-Carbon Bond, John Wiley and Sons: London, 1989; vol. 5; p 465.
4. Tsangaris, J. M.; Williams, D. R. *Appl. Organomet. Chem*. **1992**, *6*, 3.
5. Crowe, A. J. *Appl. Organomet. Chem*. **1987**, *1*, 143.
6. Crowe, A. J. *Appl. Organomet. Chem*. **1987**, *1*, 331.
7. Blunden, S. J.; Cusack, P. A.; Hill, R. *The Industrial Uses of Tin Compounds*; Royal Society of Chemistry: London, 1985.
8. Crowe, A. J.; Hill, R.; Smith, P. J. *Laboratory Evaluation of Tributyl tin Compounds as Wood Preservatives*; International Tin Research Institute: London, 1979.
9. David, S.; Hanessian, S. *Tetrahedran* **1985**, *41*, 643.
10. Patel, A.; Poller, R. C. *Rev. Sil. Ger. Tin Lead Comps*. **1985**, *8*, 263.
11. Burger, K.; Nagy, L. In *Metal Complexes of Carbohydrates and Sugar Type Ligands*; Burger, K., Ed.; Biocoordination Chemistry, Ellis Horwood: London, 1990; Chapter VI, p 236.
12. Smith, P. J. *Chemistry of Tin*; 2nd ed., Blackie Academic & Professional: London, 1997.
13. Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, Germany, 1997.
14. Guli, G.; Gennaro, G.; Pellerito, L.; Stocco, G. C. *Appl. Organomet. Chem*. **1993**, *7*, 407.
15. Nath, M.; Pokharia, S.; Yadav, R. *Coord. Chem. Rev.* **2001**, *215*, 99.
16. Gielen, M. *Coord. Chem. Rev.* **1996**, *151*, 41.
17. Tiekink, E. R. T. *Appl. Organomet. Chem*. **1991**, *5*, 1.
18. Holloway, C. E.; Melink, M. *Main Group Met. Chem*. **1998**, *21*, 371.
19. Saxena, A. K.; Huber, F. *Coord. Chem. Rev.* **1989**, *95*, 109, and references cited therein.
20. Huber, F.; Barbieri, R. *Metal Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH: Basel, 1993; p 351.
21. Clarke, M. J.; Zhu, F.; Frasca, D. R. *Chem. Rev.* **1999**, *99*, 2511, and references cited therein.
22. Barbieri, R. *Inorg. Chimica Acta* **1992**, *191*, 253.
23. Barbieri, R.; Ruisi, G.; Atassi, G. *J. Inorg. Biochem*. **1991**, *41*, 25.
24. Barone, G.; Barbieri, R.; LaManna, G.; Koch, M. H. J. *Appl. Organomet. Chem*. **2000**, *14*, 189.
25. Girasolo, M. A.; Pizzino, T.; Mansueteo, C.; Valle, G.; Stocco, G. C. *Appl. Organomet. Chem*. **2001**, *14*, 97.
26. Buza's, N.; Gyuresik, B.; Nagy, L.; Zhang, Y. X.; Korecz, L.; Burger, K. *Inorg. Chimica Acta* **1994**, *218*, 65.
27. Jansco, A.; Nagy, L.; Sletten, E. *J. Chem. Soc., Dalton Trans*. **1999**, 1587.
28. Ashfaq, M.; Khan, M. I.; Baloch, M. K.; Malik, A. *J. Organomet. Chem*. (Accepted).
29. Hopfl, H.; Sanchez, M.; Farfan, N.; Barba, V. *Can. J. Chem*. **1998**, *76*, 1352.
30. Perrin, D. D.; Armengo, W. L. F. *Purification of Laboratory Chemicals*; 3rd Ed.; Pergamon: Oxford, 1988.
31. Sisido, K.; Takeda, Y.; Kingawa, Z. Direct Synthesis of Organotin Compounds. I. Di- and tribenzyltin chloride. *J. Am. Chem. Soc*. **1961**, pp 538-541.
32. Rahman, A.; Choudhary, M. I.; Thomsen, W. J. *Bioassay Techniques for Drug Development*; Harwood Academic Publishers: The Netherlands, 2001.
33. Brian, Pw. *Trans, Brit. Mycol. Soc.* **1960**, *43*, 1.
34. Smith, Q. E. *Pharmacological-screening Test Progress in Medicinal Chemistry I*; Butter worth: London, 1960.
35. Lycka, A.; Holecek, J.; Schneider, B.; Straka, J. *J. Organomet. Chem*. **1990**, *29*, 389.
36. Shahid, K.; Ali, S.; Shahzadi, S.; Badshah, A.; Akhtar, Z. *Turk. J. Chem.* **2003**, *27*, 1.
37. Shahid, K.; Ali, S.; Shahzadi, S.; Badshah, A.; Khan, K. M.; Maharvi, M. *Synth. React. Inorg. Met.-Org. Chem*. **2003**, *33*, 1223.
38. Xie, Q. L.; Yang, Z. Q.; Jiang, L. *Main Group Met. Chem*. **1996**, *19*, 509.
39. Camacho, C. C.; deVos, D.; Mahieu, B.; Gielen, M.; Kemmer, M.; Biesemans, M.; Willem, R. *Main Group Metal Chem*. **2000**, *23*, 433.
40. Bonire, J. J.; Fricker, S. P. *J. Inorg. Biochem*. **2001**, *83*, 217.
41. Khoo, L. E.; Charland, J. P.; Gabe, E. J.; Smith, F. E. *J. Inorg. Chimica. Acta* **1987**, *128*, 139.
42. Grindley, T. B.; Curtis, R. D.; Thangarasa, R.; Wasylishen, R. E. *Can. J. Chem*. **1990**, *68*, 2102.
43. Grindley, T. B.; Thangarasa, R. *Can. J. Chem*. **1990**, *112*, 1364.
44. Blunden, S. J.; Smith, P. J.; Beynon, P. J.; Gilles, D. G. *Carbohydr. Res*. **1981**, *88*, 9.
45. Barbiere, R.; Huber, F.; Pellerito, L.; Ruisi, G.; Silverstri, A. In *Chemsitry of Tin*; Smith, P. J., Ed.; Blackie Academic & Professional: Glasgow, 1997; 496-539.
46. Buzas, N.; Pujar, M. A.; Nagy, L.; Vertes, A.; Kuzmann, E.; Mehner, H. *J. Radioanal. Nucl. Chem.* **1995**, *189*, 237.
47. Nagy, L.; Korecz, L.; Kiricsi, I.; Zsikla, L.; Burger, K. *Struct. Chem*. **1991**, *2*, 231.
48. Vertes, A.; Suveghi, K.; Kuzmann, E.; Burger, K.; Nagy, L.; Schrantz, K.; Buzas, N. *J. Radioanal. Nucl. Chem*. **1996**, *203*, 399.

49. Nath, M.; Yadav, R.; Eng, G.; Musingarimi, P. *J. Chem. Res. (M)* **1998**, 1730.
50. Nath, M.; Yadav, R.; Eng, G.; Nguyen, T.; Kumar, A. *J. Organomet. Chem*. **1999**, *577*, 1.
51. Nath, M.; Yadav, R.; Eng, G.; Musingarimi, P. *Appl. Organomet. Chem*. **1999**, *13*, 29.
52. Nath, M.; Yadav, R. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 1355.
53. Sandhu, G. K.; Kaur, G.; Holecek, J.; Lycka, A. *J. Organomet. Chem*. **1989**, *365*, 215.